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Dear Professor Sawicki:

Thank you very much for the opportunity to comment on the Consultation Draft of IQWiG's "Methods for Assessment of the Relation of Benefits to Costs in the German Statutory Health Care System." The Pharmaceutical Research and Manufacturers of America (PhRMA), an international trade association representing the world's leading research-based pharmaceutical and biotechnology companies, believes that this Draft presents a unique approach to the multi-pronged challenge of developing a standard methodology for conducting economic evaluations within statutory and other agency-defined boundaries. While this approach is compelling, it is as yet untested, and raises more questions than answers. Overall, the methods described in the draft document have not been widely vetted, tested, or substantiated with (still forthcoming) technical documentation, and therefore the document is not yet ready to be the basis for a health technology assessment in Germany.

After review of the document, it is clear that several feasibility and technical issues remain that will prevent IQWiG from performing to the maximum scientific and social benefit. These issues are described below.

***Specific Comments on Methodology***

1. "None of the existing methods… are universally accepted." This phrase on page 12 of the Draft Guidance, erroneously concludes that "there is no single set of economic evaluation standards recognized today" (Page 6). This statement largely forms the rationale for developing the novel efficiency frontier approach that the Panel took. It seems to us as an over-statement, in fact somewhat misleading. Economic evaluation of health technologies is widely done by a close-knit community of international methodologists who are basically in agreement with one another and adhere to accepted methodological principles.

2. Benefit Evaluation is Separated from Economic Evaluation: We believe that separating these two evaluations will lead to methodological problems. This is a highly unusual approach and inconsistent with well-established international practices. The concern is that the benefit evaluation may not lend itself to proper economic evaluation. In addition, since it will be accomplished therapeutic area

by therapeutic area, it may lead to unnecessary variations across therapeutic categories.

3. Efficiency Frontier Feasibility: The "efficiency frontier" is a theoretically sound concept. However, it is less clear as to whether it is operationally feasible. The methods document supposes that for a new technology to be evaluated appropriately, *all* other relevant technologies that exist on the frontier be located on that frontier in order for the frontier to be extended for price setting. It would seem likely that the "frontier" position of these other technologies will not be self-apparent, which, thus, would require separate benefit and economic evaluations for each. We question the feasibility of this process due to constraints of time, funding, and scientific staff availability. Alternatively, if the document does not assume that *de novo* valuation needs to be accomplished for all relevant technologies, it must assume near perfect knowledge that is itself unreasonable.

4. Timing across benefit and economic evaluation: As we understand it, the benefit evaluation is not to be extended beyond the timeframe of the empirical clinical data (i.e., modeling is not anticipated); however the economic evaluation is extended to the logical time endpoint (thus, likely to include modeling). To the extent this is the case, in our judgment, it will likely cause the cost-effectiveness solution to be invalid.

5. Therapeutic Boundaries: It is unclear as to how IQWiG will interpret the scope of a therapeutic class (e.g. SSRI's as a class; versus alternative methods for treating depression). For technical evaluation purposes, it would seem that narrow is better (e.g. easier, more coherent); but the narrower the boundaries the less useful for optimal societal decision-making. This needs clarification, likely debate, and one of the many elements addressed by the pilot studies suggested above.

6. Perspective: Virtually all textbooks and methodological treaties state unequivocally that the optimal and proper perspective for cost-effectiveness evaluations is the societal perspective. However, the Draft recommends a much narrower health insurer perspective. We recommend that the societal perspective be adopted as either the primary perspective or as a secondary, what has been termed by others as a "reference case."

7. Existing "Less Effective" Technologies: The methods paper proposes to evaluate only technologies that are deemed to be superior (more effective) than present ones. As a result, however, certain cost-effective technologies that do, in fact, reside on the efficiency frontier will remain unevaluated, which could lead to less optimal societal benefits and, even, less access to otherwise valued products. Also, it is not clear to what "superior" refers. A therapy that is superior in all dimensions (efficacy, safety, compliance, etc.)? Or in more than half of the important dimensions? Or is it sufficient to be superior in one dimension?

***Implementation of the Methods Document***

Even if all of the above issues were effectively addressed, we still have concerns that the outcomes of the methodology are unpredictable. Formal adoption of the draft documents should be delayed pending:

1. A pilot of the new methodology prior to adoption is necessary. Scope of pilot evaluation should include at least several diverse therapeutic areas, each one selected to illustrate different potential methodological problems. In our opinion, given all the concerns raised by methodologists and policy analysts and given the relatively novel approach that the International Expert Panel took, the present draft approach is not ready for implementation without testing.

2. Releasing all technical backup documents for external review and comments.

3. Reviewing all the comments and criticisms which are due to IQWiG later this month and (assuming this is deemed warranted based on the above) convening another group of health economists and health economic policy key opinion leaders to provide further guidance.

4. Careful consideration of the QALY method. Although maligned from time to time, especially by economic purists, the QALY has remained a reasonably useful common standard for average benefit valuation. We understand that many economists disagree with the Panel's decision to recommend a different and untested approach. We think this issue needs additional debate.

5. Adoption of an implementation plan. Although the document is fairly prescriptive, according to our sources, there are numerous ways in which it could be implemented which calls into question the evaluation of the societal and patient impact it will have. This is another important reason to conduct multiple pilot studies before formal adoption and to fix one of the most glaring omissions, the adoption of an implementation plan.

Thank you very much for considering our comments. We strongly believe that by working with the innovative pharmaceutical industry and other stakeholders, IQWiG can create a health technology assessment methodology that values innovation, ensures appropriate value for the German healthcare system, and expands the German patient's access to the most modern and effective medicines available.

Sincerely,

Brian Toohey